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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/827,255	04/05/2001	Jeffrey Tze Fei Wong	1441830001336	4343

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EXAMINER	
SCHMIDT, MARY M	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/827,255	WONG ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 8 was amended to contain the step of "delaying a cell division of cells" after administering to a subject a composition containing doxorubicin encapsulated in desialyated glycoprotein-alpha 1 coupled to a liposome. Applicant has not pointed out support for this amendment in the specification as filed. Although the specification as filed teaches making the liposome compositions containing doxorubicin encapsulated in desialyated glycoprotein-alpha 1, the specification does not specifically contemplate use of said compositions for the functions of delaying a cell division. It is not clear from this limitation what types of cell nor what stages of cell division are to be delayed, nor the nexus between administration of the liposome and any such delay in cell division. As such, the added limitation lacks written description support.

3. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for liposome compositions having PC:Chol:PS ratio of 11:4:0.025 encompassing dox coupled to alpha1 acid-glycoprotein by avidin-biotin bridges for use in cells in cell culture and in mice does not reasonably provide enablement for any liposome composition for the targeted delivery of a therapeutic agent to a tissue expressing asialoglycoprotein receptors as claimed nor methods of targeting delivery of such compositions to cells in a whole organism other than mice. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-6 and 9 are drawn to compositions that are liposome compositions specifically having the function of delivering a therapeutic agent to a tissue expressing asiologlycoprotein receptors; where the therapeutic agent is a drug or a polynucleotide; wherein the polynucleotide is a cDNA, an ribozyme or an antisense; wherein the therapeutic agent is a cytotoxic drug or a protein, such as doxorubicin, vincristine, daunorubicin, and amphiphatic amines. Claim 6 specifies the type of linkage of the desialyated glycoprotein-alpha 1 to the liposome. Claims 7-8 are drawn to a method for targeted delivery of a therapeutic agent to a tissue expressing asialoglycoprotein receptors comprising delivery to the tissue an effective amount of the composition of any of claims 1 to 6; and a method of inhibiting the proliferation of liver cancer comprising administering to a subject in need of such therapy an effective amount of a

composition containing doxorubicin encapsulated in desialyated glycoprotein-alpha 1 coupled to a liposome and delaying a cell division of cells.

The specification as filed teaches by way of example in figures 1-7 and on pages 9-13, the preparation of specific dox-containing liposomes that are conjugated to desialyated glycoprotein-alpha 1 for administration to HepG2 cells in culture and in mice.

The specification as filed is not enabled for the breath of compositions drawn to use in administration of therapeutic agents for therapeutic purposes in cells in whole organisms, with the exception of the specific liposomes taught in mice, since the specification does not teach treatment effects in cells that correlates to use in any whole organism, such as human. One example of the agents claimed for therapeutic delivery via the claimed liposomes is delivery of an antisense oligonucleotide. The following references teach why it is unpredictable in the art for administration of any antisense oligonucleotide to cells in whole organisms for therapeutic purposes:

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be

resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed for delivery of antisense.

Similarly, it would be highly unpredictable in the art to deliver any cDNA, any ribozyme, any cytotoxic drug or any protein as claimed for similar reasons. The major factors considered unpredictable for any of these compounds include: (1) formulation, (2) for proteins, size and ability to retain appropriate structure, (3) dosage and routes of administration, (4) entry into the cell, (5) toxicity, (6) desired treatment effects. Note Fritz et al. who specifically teach the barriers to successful delivery of antisense or plasmids via liposomes. They specifically teach the unpredictability in the art regarding toxicity of the nanoparticle suspensions, the stability of the liposome, the amount of ODN released, etc. On page 280 they taught that "the shape and size of

the nanoparticles play an important role for body distribution and irritant tissue reaction." On page 287, they summarize critical elements in the design of a liposome: charge, surface concentration, density, absorption behavior (the effects of the ODN modifications on these factors), enzymatic degradation, and other environmental conditions such as pH.

Since the specification as filed does not teach any specific treatment effects using the claimed compounds having a specific correlation to treatment in any whole organism, there is no guidance for overcoming the unpredictable factors in the art for making and using any therapeutic agent as claimed. One of skill in the art at the time the invention was made would have had to practice "trial and error experimentation" to make and use any of the therapeutic agents claimed for treatment effects in whole organisms such as human. One of skill in the art would necessarily practice undue experimentation to make and/use any such therapeutic agent as broadly claimed.

4. The closest prior art was taught in the previous Official Action on the merits. The 35 U.S.C. 103(a) rejection previously made has been withdrawn in view of the therapeutic requirement of the claimed compositions in favor of the above 35 U.S.C. 112, first paragraph, scope of enablement rejection.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

M. M. Schmidt
July 29, 2002